UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/019,586 | 12/20/2001 | Vanessa Chisholm | P1746R1 | 1705 |

9157 7590 11/18/2003

GENENTECH, INC.
1 DNA WAY
SOUTH SAN FRANCISCO, CA 94080

| EXAMINER | |
|---|---|
| AKHAVAN, RAMIN | |
| **ART UNIT** | **PAPER NUMBER** |
| 1636 | |

DATE MAILED: 11/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/019,586 | CHISHOLM ET AL. | |
| | Examiner | Art Unit | |
| | Ray Akhavan | 1636 | |

*-- The MAILING DATE of this communication appears on the cov r she t with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) 1-58 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-7,34-36 and 39-58 is/are rejected.

7)☒ Claim(s) 8-11,13-33,37 and 38 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

### *Priority*

It is acknowledged that instant application under 35 U.S.C. § 371. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. § 119 (e) as follows:

It is noted that this application appears to claim subject matter disclosed in prior Application No. 60/143,360, filed 07/12/1999. A reference to the prior application must be inserted as the first sentence of the specification of this application or in an application data sheet (37 CFR 1.76), if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e). See 37 CFR 1.78(a).

If the application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference to the prior application must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application.

If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121

and 365(c). A priority claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed claim for priority under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

**For the purposes of examination the granted priority date is the PCT filing date – July 11, 2000.**

***Claim Objections***

Claim 8-11, 13-33, 37-38 and 47-48 are objected to because of the following informalities: The claims are dependent on rejected base claims. Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. **Claims 7 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.**

Claim 7 is drawn to the polynucleotide of claim 1 wherein the green fluorescence protein gene (GFP) encodes a GFP-fusion protein. For a fusion protein to be produced the GFP gene would have to be in frame with a heterologous DNA fragment, thereby encoding a fusion protein. As written the claim could be interpreted to mean that a GFP gene alone is sufficient to encode fusion proteins, thus the claim is vague and indefinite. The specification discloses that a DHFR-GFP fusion gene/protein could be made using recombinant technology. (Spec. at 24, lines 35-40). It would be remedial for the claim to read "GFP-fusion gene", thus indicating that said gene encodes something other than GFP protein in and of itself.

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

**2. Claims 1-6, 34-36, 39-45 and 49-58 are rejected under 35 U.S.C. 102(a) as being anticipated by Meng et al (Gene. Jan. 2000; 242:201-7) (see whole document).**

The claims are drawn to a polynucleotide construct comprising an amplifiable gene, a green fluorescent protein (GFP) and a selected sequence encoding a desired product (i.e. target gene), where the target gene is operably linked to either the amplifiable gene or to GFP and to a promoter. Furthermore, the claims are drawn to said construct comprising a dual transcription unit, a CMV promoter, an intron placed between selected sequence and promoter, the selected sequence encoding products from a selected group of compounds including enzymes and growth factors; in addition the construct replicates in eukaryotic cells. The claims are also directed to a

method of obtaining cells expressing the desired product in eukaryotic cells using the construct of claim 1.

Meng et al. teach a polynucleotide construct comprising an amplifiable gene, a fluorescent gene and a selected gene encoding a desired product operably linked to either the amplifiable gene or to the fluorescent gene and to a promoter. (See e.g., Meng, at p. 202, § 2.1 and Fig. 2). Furthermore Meng et al. teach that the fluorescent protein can be GFP or a mutated version of GFP. (Id.) Meng et al. also teach that GFPS65T is inserted into a DHFR intron vector driven by a CMV promoter. (Id.) (referencing the intron vector as described in, Lucas et al. Nuc. A. Res. 1996; 24(9): 1774-9, at 1775) (Note: this second reference is only being cited to provide information with regard to intrinsic properties of the intron expression vector construct, See MPEP § 2131.01). In addition Meng et al. teach the selected sequence as vascular endothelial growth factor (VEGF) or dexoyribonuclease (DNase) – a growth factor and enzyme. (See e.g., Meng, Abstract and p. 204, §3.2). Further, the constructs taught replicate in eukaryotic cells, where the cells are CHO cells with a DHFR phenotype. (Meng at, 202, § 2.2).

Meng et al. also teach using the aforementioned dicistronic construct, to isolate cells expressing GFP and the amplifiable gene, with expression indicative of concomitant target gene expression. (See e.g. Meng, p. 205, col. 2, ¶¶ 2-3 and Fig. 3). Furthermore, cells were subjected to multiple rounds of FACS, comprising two week of growth in between sorting, where the amplifiable gene was DHFR and where sorting/collecting cells was based on fluorescence intensity, i.e., the brightest 0.5-5 per cent. (See e.g. Meng, p. 204, § 3.2). Selection included growing cells in increasing amounts of methotrexate, resulting in amplification obtaining higher producing clones from cells already sorted using FACS. (See e.g., Meng at 205, Col. 1, ¶ 1). In

addition cells were analyzed for RNA encoding the desired product via RT-PCR. (See e.g. Meng, p. 205, Fig. 3). Meng et al. anticipate claims 1-6, 34-36, 39-45 and 50-58.

**3. Claims 1-6 and 39-44 are rejected under 35 U.S.C. 102(b) as being anticipated by Chishima et al. (Cancer Research, May 15, 1997; 57: 2042-47) (see whole document).**

The claims are drawn to a polynucleotide comprising an amplifiable gene, a green fluorescent protein (GFP) and a selected sequence encoding a desired product (i.e. target gene), where the target gene is operably linked to either the amplifiable gene or to GFP and to a promoter. Furthermore, the claims are directed to the amplifiable gene encoding DHRF and the GFP is further limited to mutant GFP – S65T. The invention is further directed to cells and a kit comprising the polynucleotide with the aforementioned characteristics.

Chishima et al. teach an expression construct where a GFP gene (S65T) is mobilized into a dicistronic expression vector comprising an amplifiable gene (i.e. DHFR) and a gene expressing a desired product. (Chishima, at 2042, col. 2, ¶3, referring to the pED-mtx$^r$ construct described in, Kaufman et al. Nucleic Acids Research. 1991; 19(16):4485-90) (Note: this second reference is only being cited to provide information with regard to intrinsic properties of the pED-mtx$^r$ expression construct not as additional art, See MPEP § 2131.01). Kaufman et al. teach that the pED-mtx$^r$ construct contains a gene encoding a desired product operably linked to a promoter (i.e. B-lactamase gene, Kaufman, at 4487, Fig. 1). Chishima et al. further teach that the construct replicates in CHO cells. (Chishima, at 2042, col. 2, ¶4).

Although Chishima does not explicitly state that the CHO cells are of a DHFR$^-$ phenotype Chishima teaches that growth medium containing MTX is used to select for cells

transformed with DHFR-gene-containing vectors (Chishima, at 2042, col. 2, ¶ 4). Cells that are $DHFR^-$ will not grown in MTX-containing mediaum; This information is enough to convey to one skilled in the art that the CHO cells used, have a $DHFR^-$ phenotype, because only cells transformed with the DHFR gene vector are able to grow in medium that selects for $DHFR^+$ phenotype. Therefore Chishima anticipates claims 1-6, 39-44.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

**4. Claim 46 is rejected under 35 U.S.C. 103(a) as being unpatentable over Meng et al. (Gene, Jan. 2000; 242: 201-7) (See whole document).**

It would have been obvious at the time of the invention to package the DNA in a container so as to preserve it or protect it from degradation, prior to using the vector. One would have been motivated to do so in order to store and protect the vector and prevent its degradation.

**5. 47-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meng et al. (Gene, Jan. 2000; 242: 201-7) (See whole document) further in view of Moir and Mao (Bioprocess Technol. 1990; 9:67-94)(See whole document) or Lubiniecki and Lupker (Biologicals. 1994, 22(2): 161-9)(See whole document).**

The claims are drawn to a method of producing a target protein comprising introduction of a dicistronic expression construct into a suitable eukaryotic cell and recovering the desired protein product from the cell or from the culture medium. The claims are not drawn to any particular method of recovery, but rather only indicate that the desired protein is recovered. In addition claim 46 is drawn to a kit containing the polynucleotide of claim 1.

With regard to claims 47 and 48, Meng et al. teach a method of quickly and efficiently selecting cells expressing a desired product in a cell system using dicistronic expression system (i.e. applicant's claim 1). (See e.g. Abstract). Although Meng et al. comment that cells are often used for expression of recombinant proteins, there is no explicit mention that the desired protein product can be recovered from cells or from the culture media.

Moir and Mao teach that proteins of interest can be produced and targeted to different compartment of cells within which they are produced or secreted into the culture medium using secretory pathways of yeast and mammalian cells. (See e.g. p. 67, ¶1). Moir and Mao explicitly state that protein products from exogenously added genes on recombinant vectors can be targeted to the culture medium for production (i.e. recovery) of industrially important proteins. (Id., ¶¶ 1-3). Furthermore, Lubiniecki and Lupker teach that recombinant proteins produced in an animal cell culture system can be purified using chromatography techniques known in the art to medicinal quality. (p. 167, ¶ 3).

The ordinary skilled artisan seeking to produce proteins for biotechnology or pharmaceutical applications in cell culture systems would have been motivated to combine the teachings of Meng et al. – an expression system designed to express proteins of interest in addition to FACS sorting – with the teachings of Moir and Moi or Lubiniecki and Lupker – using cell culture systems combined with standard chromatography techniques to purify (i.e. recover) proteins of interest, with the added benefit of FACS sorting. The whole point of Meng et al. is to select cells that are producing proteins, thus would have been obvious for the ordinary skilled artisan to incorporate the selection/expression system of Meng et al. to express proteins that could then be purified or recovered.

Given the teachings of the cited art and the level of skill of the ordinary skilled artisan at the time of applicant's invention, it must be considered that the skilled artisan would have had a reasonable expectation of success in making recombinant protein to be recovered from a cell culture system using applicant's selection/expression system.

***Conclusion***

The claim for priority is defective. Claims 1-7, 34-36 and 39-58 are rejected. Claims 8-11, 13-33 and 37-38 are objected to as being based on rejected claims, but may be allowable if rewritten in independent format with all the limitations of base and intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ramin (Ray) Akhavan whose telephone number is 703-305-4454. The examiner can normally be reached on 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D., can be reached on 703-305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.
Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1123.

***